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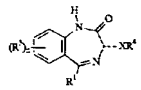
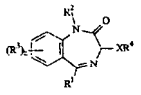
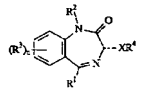
(54) Title: PROCESS FOR PREPARING BENZODIAZEPINES



(I)



(IIa)



(II)

(57) Abstract: A process for producing a compound which is a benzodiazepine derivative of formula: (I) wherein: represents or $R^1$ represents $C_{1-6}$ alkyl, aryl or heteroaryl; each $R^3$ is the same or different and represents halogen, hydroxy, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkoxy, amino, mono($C_{1-6}$ alkyl)amino, di($C_{1-6}$ alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$, $-S(O)NR'R''$ or $-S(O)_2NR'R''$, wherein each R′ and R″ is the same or different and represents hydrogen or $C_{1-6}$ alkyl; n is from 0 to 3; X represents -NH-, -N($C_1$-$C_6$alkyl)-, -CO-, -CO-NR′-, -S(O)- or $-S(O)_2$-, wherein R′ is hydrogen or a $C_1$-$C_6$ alkyl group; and $R^4$ represents hydrogen; or $-CO-R_4$' or -CO-NH-$R^{4'}$, wherein $R^{4'}$ is a $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, aryl, heteroaryl, carbocyclyl or heterocyclyl group, which group is substituted by a $C_1$-$C_6$ hydroxyalkyl, aryl, heteroaryl, carbocyclyl or heterocyclyl group or a -($C_1$-$C_4$ alkyl)-$X_1$-($C_1$-$C_4$alkyl)-$X_2$-($C_1$-$C_4$ alkyl) group, wherein $X_1$ represents -O-, -S- or -NR′-, wherein R′ represents H or a $C_1$-$C_4$ alkyl group and $X_2$represents -CO-, -SO- or $-SO_2$-; or $R^{4'}$ represents $-A_1$-Y-$A_2$, wherein: $A_1$ is an aryl, heteroaryl, carbocyclyl or heterocyclyl group; Y represents a direct bond or a $C_1$-$C_4$ alkylene, $-SO_2$-, -CO-, -O-, -S or -NR′-, wherein R′ is a $C_1$-$C_6$alkyl group; and $A_2$ is an aryl, heteroaryl, carbocyclyl or heterocyclyl group; or $R^4$ is a group selected from aryl-C(O)-C(O)-, heteroaryl-C(O)-C(O)-, carbocyclyl-C(O)-C(O)-, heterocyclyl-C(O)-C(O)- and $-ZR^5$, wherein: Z represents -CO-, -S(O)- or $-S(O)_2$-; and $R^5$ represents $C_{1-6}$ alkyl, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl-($C_{1-6}$ alkyl)-, heteroaryl-($C_{1-6}$ alkyl)-, carbocyclyl-($C_{1-6}$ alkyl)-, heterocyclyl-($C_{1-6}$ alkyl)-, aryl-($C_{1-6}$ alkyl)-O-, heteroaryl-($C_{1-6}$alkyl)-O-, carbocyclyl-($C_{1-6}$ alkyl)-O-, heterocyclyl-($C_{1-6}$ alkyl)-O- or -NR′R″ wherein each R′ and R″ is the same or different and represents hydrogen, $C_{1-6}$ alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl-($C_{1-6}$ alkyl)-, heteroaryl-($C_{1-6}$alkyl)-, carbocyclyl-($C_{1-6}$ alkyl)- or heterocyclyl-($C_{1-6}$ alkyl)-; or a pharmaceutically acceptable salt thereof; which process comprises: (a) subjecting a racemic benzodiazepine derivative of formula: (IIa): wherein $R^1$, $R^3$, $R^4$, n and X are as defined above, and $R^2$ represents an amino protecting group, to crystallisation induced dynamic resolution to yield a benzodiazepine derivative of formula (II): wherein, $R^1$, $R^2$, $R^3$, $R^4$, n and X are as defined above; and (b) deprotecting the benzodiazepine derivative of formula (II) as defined above to yield a benzodiazepine derivative of formula (I) or a pharmaceutically acceptable form thereof as defined above.

WO 2005/090319 A1

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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*